REMARKS

The undersigned attorney thanks Examiners Kosar and Gupta, and Supervising Primary Examiner Tsang, for the telephonic interview that took place on February 4, 2009. During the interview the undersigned discussed his reasoning and basis for his belief that the amended claims previously sent via e-mail attachment to Examiner Kosar for discussion purposes (and which are now offered formally in slightly altered form), define novel, unobvious, and useful subject matter that is fully supported in the specification, and that they particularly point out and distinctly claim the subject matter which applicant regards as his invention as required by the second paragraph of 35 USC 112.

The undersigned also discussed with the Examiners that many dosage forms can be devised by persons of skill in the art to achieve this blood concentration, and that it was critical to protect Dr. Fein's invention to obtain a low dose desmopressin claim that was unlimited with respect to the chemical or mechanical way the dosage form worked. The important characteristic of the dosage form is that it is necessarily effective to achieve the stated blood concentration range for some desired relatively short period of time, irrespective of how it does so. Applicant's invention does not lie in the particular way (mechanical or chemical) one achieves the blood concentration range. Applicant has limited his claims to certain dose forms convenient for self-administration out of a depth of caution so as to exclude oral, subcutaneous, and intra venous dosage forms and to avoid potential anticipations from possible unknown sources not of record.

After the original interview, the undersigned conducted a second interview on Feb 4, 2009, with Quality Assurance Specialist Robert Wax. The substantive content of these interviews, together with Applicant's arguments for patentability of the claims as amended, is set forth below.

Reconsideration and withdrawal of all rejections is respectfully requested in view of the amendments offered above and the following argument.

Summary of Action

All previous rejections, both art-based and 112 rejections, were overcome in the previous response, and the Examiner has made new rejections based on one piece of new (although

previously cited) art and two patents previously of record. Claims 1, 3, 4, 9 and 27-31 now are rejected as anticipated by FJELLESTAD-PAULSEN. Claims 29, 30, 32 and 33 are rejected as anticipated by SIBALIS. Claims 29, 30, 32 and 33 are rejected as anticipated by BANNON. Claims 1, 3, 4, 6, 7, 9 and 27-33 are rejected as being unpatentable for obviousness under 35 USC 103 over FJELLESTAD-PAULSEN, in view of SIBALIS or BANNON. Also, all claims are provisionally rejected for double patenting.

The Claim Amendments

Entry of the foregoing amendments is respectfully requested as they place all claims in condition for allowance or at least put them in better form for appeal.

Based on a reading of the outstanding office action rejecting the pending claims, the undersigned suspects that the "adapted for" and "sufficient to" language may have been considered by the PTO to be insufficiently limiting and therefore to leave the claims open to cover the prior art dosage forms described in the references applied in the office action. While Applicant disagrees with this position, he nevertheless proffers the amendment above to delete the "adapted for" language and to insert language requiring more explicitly that the dose forms when properly administered *must* establish the concentration range recited. Thus, all of the claims as amended affirmatively recite specific types of dosage forms and *require* that they establish serum concentrations within the critical range. This amendment raises no new substantive issues, and accordingly, entry is requested.

The Seriousness of Hyponatremia

In his office action the Examiner quotes from the Fjellestad-Paulsen thesis to the effect that "numerous studies have confirmed the superiority of dDAVP in the treatment of central or neurogenic diabetes in both adults and children *because of its prolonged antidiuretic effect and lack of side effects*" (emphasis added) and goes on to reference sections indicating the drug has been used to treat "nocturia in adults."

Applicant notes that this is a superficial and rosy description of the utilities of conventional doses of desmopressin not consistent with historical facts. Ferring, the desmopressin innovator company, has attempted to gain approval for dDAVP use for the treatment of adult nocturia in the European Union, and has conducted clinical studies, so to that

extent desmopressin has been "used" to treat nocturia in adults. However, Ferring's application has been rejected in at least the United Kingdom, France, Germany, and Italy, and the company has declined to try to gain approval in the United States. All of these refusals were based on study results that showed an *unacceptable risk of hyponatremia* and consequent lack of safety. Furthermore, the "prolonged antidiuretic effect" said by Fjellestad-Paulsen to be an advantage of such conventional dose forms, plays a central part in this unacceptable safety profile. It is accordingly quite ironic that the doses are said to "*lack ... side effects.*"

Still further, the US Food and Drug Administration has issued a warning to physicians that desmopressin should not be used to treat PNE (juvenile bed wetting) except in extreme circumstances. This "Black Box" warning[1] came on the heels of tragic and unfortunate deaths of children from hyponatremia.

Nothing in the Fjellestad-Paulsen thesis so much as recognizes this objectively very serious side effect, much less how to use the drug while avoiding it.

The Obviousness Rejections

As stated and discussed in the interview, Applicant submits none of the newly applied references disclose that the desmopressin doses they disclose can or necessarily do deliver desmopressin to produce blood concentrations less than about 10 pg/ml. Furthermore, none of the references suggest that it may be desirable to, or there is any advantage to, make a dose form that will deliver the recited concentration, and all presented claims, one way or another, require that dose forms falling with in the claims *must establish a blood concentration in the recited low dose ranges.*

To reiterate Applicant's argument presented during the interviews, the claims are directed to certain low dose forms of a known drug, desmopressin, which have been discovered to have unobvious and very valuable properties. The dose forms, among other advantages, serve to

[1] FDA notified healthcare professionals and patients of the Agency's request that manufacturers update the prescribing information for desmopressin to include important new safety information about severe hyponatremia and seizures. Certain patients, including children treated with the intranasal formulation of the drug for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatremia that can result in seizures and death. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

minimize or eliminate the chances of the patient developing hyponatremia and serve to regulate the duration of the known antidiuretic effect of the drug. No prior art known to the undersigned attorney suggests that it is possible to decouple desmopressin's hyponatremia-inducing effects from its antidiuresis effects, nor suggests the desirability or possibility of controlling the duration of antidiuresis induced by the drug. Certainly, none of the three applied references suggest that either goal is possible, much less how to obtain it.

Accordingly, the outstanding obviousness rejection of the claims, to the extent applied to the claims as amended, is clearly improper. The subject matter claimed, taken as a whole, and including its inherent properties, simply were not understood or obvious to a person of skill in the art before applicant made his invention.

During the interview the undersigned urged that the invention had experienced significant success, noting that it has opened up the possibility of new, safe, therapies for managing nocturia, various forms of incontinence, and similar urination related health problems, that a successful phase two clinical trial of an intranasal dosage form has just been completed, and that several pharmaceutical companies were conducting diligence on the drug opportunity. The Examiners correctly stated that those arguments are relevant only to an obviousness rejection, and not to an anticipation rejection, the issue at hand. From this, the undersigned assumes that his arguments have overcome the outstanding obviousness rejection, and requests acknowledgement that it is withdrawn.

The Anticipation Rejections

During the initial interview, and then again during the discussion with Mr. Wax, it became apparent that the Examiner's anticipation rejections were based on inherency, and this in turn was based on the proper interpretation and effect of the claim limitation:

> "which when administered to a patient in accordance with packaged instructions establishes a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per ml plasma/serum to about a maximum of 10.0 picograms desmopressin per ml plasma/serum . . . ."

While the Examiners objected to the functional aspect of this language, it is well established that there is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). "A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used." MPEP section 2173.05(g). Accordingly, it is improper to ignore the functional limitations of a claim during examination. The law is clear that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the art. However, there is no prohibition to the use of functional language to define a *novel subgenus*, where, as here, that subgenus is characterized by new and unanticipated properties.

Of course, a proper anticipation rejection requires that a reference disclose "within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim." *Net MoneyIN, Inc. v. Verisign, Inc.*, (Fed. Cir. 2008) This is a question of fact. Clearly, none of the applied reference meet this test *explicitly*, and the Examiners during the interview explained that the anticipation rejections were based on *inherency*. They noted that if a prior art composition is physically the same as a claimed composition, it must inherently have the same properties. The undersigned attorney urged that this, while true, had no application to the rejection at hand, because the dose forms in the applied prior art are *not the same* as those claimed.

In this regard, Applicant reminds the Examiner of the Nardi declaration, of record herein. In that declaration Dr. Nardi addressed the Examiner's statement that administration of the desmopressin pharmaceutical compositions disclosed in then applied references would:

> "inherently provide the instantly claimed functional effect upon administration" in that, if the desmopressin formulations taught by the references were administered in a proper form, "a steady plasma/serum desmopressin concentration within the approximate instantly claimed range, as well as a decrease in urine production, would inherently occur."

Regarding this assertion, Dr Nardi stated:

10. The bioavailability of a drug is defined as the amount of drug taken or administered that actually reaches the circulation and therefore can have a physiological effect. For desmopressin, which is a peptide hormone analog, oral, transmucosal, and transdermal bioavailability is poor because only a small fraction of the drug administered is able to reach a patient's bloodstream through the gastrointestinal tract, across mucosal tissues of the mouth or nasal passages, or through the skin. I believe the currently accepted oral bioavailability of desmopressin is about 0.08% to 0.12%, (see Monograph, page 5, Table 2). This bioavailability is low because peptides are inactivated by digestion in the stomach and the completeness of the digestion varies, influenced by many factors, including diet. Intranasal bioavailability of the currently available desmopressin product is about 3% to 4%, (see Monograph, page 5, Table 2). Oral transmucosal bioavailability of desmopressin is in the range of 0.25%. This range is low and very broad as the oral mucosal (buccal) surface area and permeability vary among individuals, and because the dwell time of any dosage form in position adjacent the membranes in the mouth varies widely, with unknown amounts of the active in conventional buccal dosage forms being diluted in saliva and swallowed, and essentially lost by digestion in the stomach. Transdermal bioavailability is dependent on many formulation factors known to the skilled artisan. Subcutaneous, intramuscular, intra-arterial, and intravenous delivery modalities have a bioavailability of essentially 100%.

11. When bioavailability is taken into account, it is apparent that none of the cited references disclose an intranasal, transmucosal, transdermal, conjunctival, or intradermal dosage form that inherently achieves a steady plasma/serum desmopressin concentration in the range required by the claims. All of the dosages I have seen described in the applied art result in a serum concentration in excess, and typically far in excess, of the concentration range recited in the claims. While it is possible to formulate low dosage forms if one sets out to achieve such a sustained low concentration, none of the cited references make any such attempt. The reason for this perhaps is that, at such low serum concentrations, desmopressin has been thought to be ineffective to interrupt urine production significantly."

Applicant accordingly submits that intranasal, transdermal, and intradermal desmopressin dose forms comprising 0.5 ng to 20 µg desmopressin and a pharmaceutically acceptable carrier, when used, *do not necessarily produce the same drug concentration in plasma/serum.* The connection between the amount of drug in the dose form, and the blood concentration achieved by the dose form, is dependent on *bioavailability*, as Dr. Nardi states, and this can be tested for and modulated by the artisan via selection and formulation of excipients, spray patters, solvents, permeation enhancers, patch area, release rate, etc., engineered into the dose forms.

There is an important difference between, on the one hand, the concentration of the active in the dose form, and on the other, blood/plasma concentration achieved. Intranasal dosage forms, for example, can have a variety of amounts of active and concentrations of active that

enter the nostril, and an independent variety of blood concentrations achieved, depending on many factors that determine how much of the active actually reaches the blood stream. During the interview the undersigned attorney explained (and the Examiners appeared to agree) that there are many ways to adapt conventional formulation technology so as to achieve the blood concentration recited in the claims (which is far *lower* than conventional clinically used doses), and that persons of skill in the formulation art can make many embodiments of the invention. Again, Applicant submits that the details and mechanics of how one goes about devising a dose form that delivers this low concentration is not an aspect of his claimed invention.

Applicant submits that none of the references now applied meet the requirements for a proper 102 rejection based on inherency. Furthermore, this is submitted to be so clear that no additional declaration evidence is required to establish the pertinent facts.[2]

Note MPEP section 2112, part IV, Requirements of Rejection Based on Inherency – Examiner Must provide Rationale Or Evidence Tending To Show Inherency, quoted in part below (underlining supplied, italics in original):

> "The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) * * * Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the

[2] Applicant offers to submit on an expedited basis declaration evidence supporting any assertions of fact herein considered by the PTO to be in issue.

claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

Applying these requirements to the applied references, unless one improperly ignores the express claim requirement that the dose forms must establish the low dose blood concentration, none meet these clear standards. The dosage forms discloses in the applied prior art, fundamentally, are insufficiently described to permit determination of the blood concentration they produce, or they could be made to create essentially any blood concentration. There is no disclosure in these references of a dose form that necessarily will produce the recited blood concentrations, no disclosure that one should formulate so as to establish a blood/plasma concentration within the claimed range, and none that teaches any criticality or importance of any concentration.

Turning now specifically to the newly applied references, the Examiners assert that each independently inherently anticipate the claims. To meet their burden, as the law requires:

- the extrinsic evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill;
- inherency may not be established by probabilities or possibilities;
- The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency; and
- To establish inherency the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.

Fjellestad-Paulson This student thesis discusses oral, intravenous, subcutaneous, intranasal, and other desmopressin dose forms. Patch technology for administering the drug is not apparently discussed, so the only teaching possibly relevant to the anticipation of the subject matter claimed herein is the *intranasal* data. Study III and Study VI involve intranasal dosing.

At page 14 in the background section the thesis states "The most prevalent route of administration [of desmopressin] is the intranasal (i.n.). Children and adult patients usually require 5-20 μg dDAVP intranasally once or twice daily (Robinson 1976) and infants are treated with smaller doses ranging from 1-15 μg once or twice a day (Kauli et al, 1985)." The concentration of desmopressin that is produced in the blood stream of the respective patients is dependent on the bioavailability of the intranasal formulations, on the amount of desmopressin in the dose, and on the weight (amount of plasma/serum) of the patients, which is not specifically disclosed for these doses. There is a clear indication that children are given proportionately less drug than adults, which is standard clinical practice.

At page 16, the thesis discusses intranasal bioavailability, and states that it varies for small peptides "between 1 and 12 %" and that in one desmopressin study "the bioavailability was 10%" and another "found a bioavailability as low as 2% after i.n. administration." Page 25 provides a table comparing oral and intranasal administration of desmopressin. All of the i.n. dose forms were given twice daily, and provided 5 + 5, 5 + 10, or 10 + 10 μg dDAVP. At page 26, under materials and methods, the author states that for study III, a 10 μg intranasal dose was used, and that study VI employed an "intranasal solution containing 100 μg /ml and was given by a calibrated rhinyle catheter." *No data are provided from which blood concentration produced by these dose forms could be known. No data are provided which would permit replication of the experiments so as to enable measurement of desmopressin blood concentration.*

The pharmacokinetic study (study III), compares the bioavailability of different dose forms. The intranasal dose studied delivered 20 μg into the nostrils (10 in each, see page 37 line 6). According to the plot on page 37 of the reference, this produced a blood concentration that started at about 10 *picomoles per liter*, moved up to about 18 or so after 1/2 hour, and decreased below 10 picomoles per liter for the first time at four hours. The error bar on these data appear to be roughly +/- 8 picomole per liter; the study included "8 healthy humans" (see page 24-materials and methods), but no data is presented as to how many subjects were administered the various dose forms. In any event, to convert picomole per liter to *picograms per ml*, one must divide by 1000 (to convert liters to milliliters) and multiply by the molecular weight of desmopressin (1069). Accordingly, after the conversion the data points are about 1.07 times *higher* than depicted in the graph.

This means that the test intranasal dose reportedly produced a blood concentration almost two times higher than the maximum permitted by the claim limitation.

The Examiner cites in his office action the subcutaneous dose of 2 μg (asserted to be the equivalent of intradermal). According to the graph on page 37, that dose form (which is not within the claims) produces a blood concentration at least about four times greater than the maximum permitted by the claims. In his rejection the Examiner states that "nothing precludes intradermally injecting the [2 μg desmopressin] NaCl composition." This statement can be conceded, but does not support an anticipation rejection. It refers to a *possibility*, not a *necessity*. Furthermore, if this step were taken it would not necessarily produce the requisite blood concentration unless by chance injecting intradermally instead of subcutaneously happened to reduce bioavailability just enough to reduce blood concentration to the range required.

Applicant submits this reference, on its face, meets *none of the requirements* for inherency. The extrinsic evidence *does not* make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference; at best the examiner has shown a *possibility* that the dose forms described may produce the requisite blood concentration; the mere fact that a certain thing (here the blood concentration) *may* result from a given set of circumstances is not sufficient to establish inherency; and the Examiner has not shown that the allegedly inherent characteristic *necessarily* flows from the teachings of this applied prior art.

Sibalis This patent discloses a current-driven transdermal patch for delivering peptides to the circulation. Representative peptides include desmopressin. The only data relevant to concentration is in the examples, none of which involve desmopressin and none of which found it necessary to mention any blood concentration. Example 2, however, speaks of transdermal transport of 60 and 200 μg per hour of a ten unit peptide. If this amount of desmopressin were delivered to the blood stream, it would yield a massive dose far in excess of the range required in the claims herein. "Model example 1" describes delivery of lypressin from a 6 ml reservoir comprising 0.185 mg (or 185 μg) per ml lypressin. There is no data relevant to the blood concentration of the drug in the dogs. Model examples 2 and 3 are no more helpful.

Applicant submits this reference, on its face, meets *none of the requirements* for inherency.

Bannon This patent discloses a transdermal device for delivering a drug substance to the circulation, including desmopressin. As the Examiner notes, Example 5 describes a composition comprising 3 mg/ml desmopressin. This example is said to be a repeat of example 1, but substituting the desmopressin composition for the nicotine composition of example 1, which involved an unspecified amount of a solution apparently containing 55 mg/ml nicotine. In Example 1, the transport of nicotine through cadaver skin was tested, and the results are depicted in Figure 3 of the patent. That figure shows nicotine release vs. time, and that the driving current apparently was not turned on for five hours, at which time the amount released was already about a third of a milligram, or about maybe 300 μg. After activation of the patch the nicotine release escalates to 3 milligrams. There is no data presented for the desmopressin release rate. That this described desmopressin dose form would necessarily and therefore inherently meet the blood concentration limitation of the claims presented herein is *speculation*. Applicant submits this reference, on its face, meets *none of the requirements* for inherency.

Provisional Obviousness-type Double Patenting Rejections

Claims 1, 3, 4, 6, 7, 9 and 27-33 were *provisionally* rejected for obviousness-type double patenting as allegedly unpatentable over claims of later-filed, co-pending applications 12/173,072 and 12/173,074. In accordance with MPEP § 804 (I)(B)(1), Applicant understands that this provisional rejection will be withdrawn once all other outstanding rejections have been overcome.

If the Examiner believes that a telephone conversation with Applicant's attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney at (617) 570-1780.

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